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Evaluation of intraductal breast papilloma based on immunohistochemical analysis of p16, p53 and ki-67

Intraductal papilloma of breasts

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Abstract
Aim: This study aimed to evaluate preoperative features, postoperative outcomes, and the positivity rates of immunohistochemical staining with p16, p53 and Ki-67 in patients undergoing surgery for intraductal papilloma.
Material and Methods: The study included 33 patients aged >18 years, diagnosed with intraductal papilloma between 2011 and 2020. Data about demographic features (age and gender), clinical picture, results of pathological examinations (if present), type of surgery, and immunohistochemical staining with p16, p53 and Ki-67 were obtained. In addition, the patients were divided into 2 groups: <50 years (Group1), ≥50 years (Group2). These 2 groups were compared in terms of the abovementioned parameters.
Results: All patients were female, with a mean age of 49.75 years. Papilloma rates were equal in right and left breasts. Discovery of a mass was the most common cause for presentation (72.7%). P16 and p53 were positive in Group1 and Group 2, with rates of 90.9% and 81.8%, respectively, and the mean Ki-67 index was 2.7. All patients aged <50 years were stained with p16. The distribution of p53staining was similar in both groups (p=0.817). The mean Ki-67 index was higher in women aged >50 years (2.1 vs 3.8) (p=0.018).
Discussion: This study showed high rates of p16 and p53 positivity in patients with intraductal papilloma. Although there was no difference in the distributions of p16 and p53 between the groups, the Ki-67 index was higher in patients aged >50 years. Multicentre studies with long-term follow-ups are needed to reveal the prognostic importance of tumor-suppressing genes such as p16 and p53.

Keywords
Papilloma, p16, p53, Ki-67, Breast

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Introduction

Intraductal papilloma is a benign tumor localized in the ducts of the breasts. It is caused by abnormal growth of ductal epithelial cells. Histologically, intraductal papilloma is characterized by a fibrovascular nucleus lined with both epithelial and myoepithelial cells [1].

P16, also called p16INK4a, is a cyclin-dependant kinase inhibitor 2A. It is a protein that reduces cell division and functions as a tumor suppressor by slowing the cell cycle from the G1 phase to the S phase. Mutations of tumor-suppressing gene p53 are the most common genetic abnormality in human cancers. Therefore, high concentrations of p53 accumulation are a potential sign of malignancy and can be associated with a poor prognosis in some types of tumors. The Ki-67 antigen is a marker of cell cycle and proliferation; it is usually utilized to predict proliferation and shows cellular growth rate [2,3].

Objective etiological factors in intraductal papilloma are not yet clear; therefore, evaluating immunohistochemical expressions like p16 and p53 will be beneficial. Nevertheless, there have been few studies about this issue in the literature [4,5].

The present study evaluated preoperative features, postoperative outcomes, and positivity rates of immunohistochemical staining with p16, p53 and Ki-67 in patients undergoing surgery for primary intraductal papilloma.

Material and Methods

Data related to patients undergoing surgery for intraductal papilloma in the general surgery clinics of Adana City Training and Research Hospital between 1 July 2011 and 31 October 2017 and in the general surgery clinics of Adana City Training and Research Hospital between 31 October 2017 and 15 November 2020, and were gathered from the relevant hospital electronic databases and patient files and retrospectively analyzed.

The inclusion criteria were age >18 years and intraductal papilloma diagnosis. The exclusion criteria were incomplete treatment, missed post-surgery follow-up appointments, missing data, and age <18 years. Data on demographic characteristics (age and gender), clinical presentation, pathological features (if present), and type of surgery were collected from both electronic databases and patient files from the hospitals. Immunohistochemical staining with p16, p53 and Ki-67 was performed on specimens available in the pathology laboratories. Obtained data were compared between women aged 18–50 years and those aged ≥50 years.

The study was approved by the hospital's institutional review board (IRB No. 22.04.2021/79/1375). Since the study was retrospective, patient consent could not be obtained.

Statistical Analyses

Data were analyzed using Statistical Package Program for Social Sciences 25. Data on categorical variables were expressed in numbers and percentages, and data about continuous variables were expressed as mean and standard deviation (in the median and minimum–maximum values, when necessary).

Results

The study included 33 female patients with a mean age of 49.75 years. Papilloma rates were equal in right and left breasts. Mass

Table 1. Patient Demographic and Clinical Features

	n	
Age mean ±SD	33	49.75±13.8 50 (18–70)
Gender		**%**
Female	33	100
Location		
Right breast	17	51.5
Left breast	16	48.5
Symptom		
Mass	24	72.7
Hemorrhagic discharge	6	18.2
Incidental	3	9.1
Type of Surgery		
Tru-Cut	8	24.2
Excision	22	66.7
In specimen obtained through mastectomy, staining with:	3	9.1
p16		
0 (<5%)	3	9.1
1 (5%–25%)	16	48.5
2 (25%–75%)	11	33.3
3 (≥75%)	3	9.1
p53		
0 (<5%)	6	18.2
1 (5%–25%)	17	51.5
2 (25%–75%)	10	30.3
3 (≥75%)	0	0
Ki-67	33	2.7±3.1

Table 2. Comparison of Tumour Location, Symptoms, Type of Surgery, and Staining with p16, p53 and Ki-67, between Age Groups

	<50 years (%)	≥50 years (%)	p
	n:13	n:20	
Tumor Location			
Right breast	7(53.8)	10(50)	0.556
Left breast	6(46.2)	10(50)	
Symptom			
Mass	13(100)	11(55)	0.018
Hemorrhagic discharge	0	6(30)	
Incidental	0	3(15)	
Type of Surgery			
Tru-Cut	4(30.8)	4(20)	0.309
Excisional biopsy	9(69.2)	13(65)	
Mastectomy	0	3(15)	
p16			
0 (<5%)	0	3(15)	0.383
1 (5%–25%)	7(53.8)	9(45)	
2 (25%–75%)	4(30.8)	7(35)	
3 (≥75%)	2(15.4)	1(5)	
p53			
0 (<5%)	3(23.1)	3(15)	0.817
1 (5%–25%)	6(46.2)	11(55)	
2 (25%–75%)	4(30.8)	6(30)	
3 (≥75%)	0	0	
Ki-67	2.1±2	3.8±4.1	0.018

was the most common symptom upon presentation (72.7%). The most common type of surgery was surgical excision (66.7%). P16 and p53 were positive (to varying degrees) in 90.9% and 81.8% of Group 1 and Group 2, respectively, and the mean Ki-67 index was 2.7. Patient demographic and clinical features are presented in Table 1.

Out of 33 patients, 20 were aged ≥50 years and 13 were aged <50 years. The rate of patients presenting with a mass was higher in Group 2 (100%) than Group 1 (55%) (p = 0.018). P16 was positive in all patients aged <50. The distribution of p53 positivity was similar in both groups (p = 0.817); however, the Ki-67 index was higher in patients aged >50 years (2.1 vs 3.8) (p = 0.018). Table 2 shows the distributions of p16 and p53 positivity, and Ki-67 index, by age groups.

Discussion

Papillary lesions of the breast vary from benign intraductal papilloma to invasive carcinoma. They are found during autopsy in 35% of women aged 20–54 years. Intraductal papilloma accounts for less than 10% of benign breast lesions and less than 1% of malignant breast tumours [6]. Clinically, they may present with spontaneous nipple discharge or a palpable mass; however, most of them are detected in routine screenings [7]. The mean age of patients in the present series was 49 years, which is consistent with the literature. In addition, as expected, symptoms on presentation were mass and nipple discharge. Patients aged >50 years were routinely screened, and some patients were diagnosed with intraductal papilloma during screenings.

The American Society of Breast Surgeons, in its consensus guidelines for managing high-risk lesions, recommends that most intraductal papillomas without atypia be removed. However, it is stated that the decision to remove lesions should be individualized, considering lesion size, symptomatology, palpability, and breast cancer risk (available at: https://www.breastsurgeons.org/resources/statements). In the present series, 75.8% of patients were treated with surgical excision, as recommended in the guidelines.

Breast cancers represent complex and heterogeneous diseases with unclear etiology. The molecular events involved in the transformation from benign intraductal papilloma into malignant lesions are still largely unknown. Prior studies have shown a relationship between the prognosis of breast carcinoma and p16 and p53. However, the roles of p16 and p53 in breast cancer subtypes have not been thoroughly described [8,9,10]. In addition, in intraductal papilloma, the expression and prognostic importance of p16 and p53 are unclear.

In a series of 400 cases, Shan et al. evaluated the expression and prognostic importance of p16 and p53 in several breast cancer subtypes. They found that p16 was more downregulated (had low expression) in luminal-A subtypes of ductal carcinoma in situ compared to subtypes of other breast cancers. An analysis of the correlation between p16 and p53 in several breast cancer subtypes revealed that when p16 was downregulated, immunohistochemical staining with p53 was negative only in luminal-A subtypes of ductal carcinoma in situ. P16 is clearly important in luminal subtypes, and especially the luminal-A subtype. This marker is closely related to a favourable prognosis. P53 also plays an essential role in subtypes of triple-negative breast cancer. P16 and p53 have different roles in different subtypes of breast cancer. It has been shown that p16 expression in luminal-A subtypes can be associated with progression from ductal carcinoma in situ to invasive ductal carcinoma, and both p53 and p16 expressions are essential in terms of triple-negative breast cancer development in cases of ductal carcinoma in situ and invasive ductal carcinoma [8].

In a systematic review, da Costa et al. analyzed 12 studies showing p53 expression in women diagnosed with benign breast disease. Most of the selected studies focused on the analysis of p53 expression in breast tissue with non-proliferative lesions. When all types of breast tissue were compared, 34.39% of patients with benign breast disease showed p53 expression [11]. In the current series, 81.8% of patients with benign breast disease showed p53 expression, which is higher than reported in the literature.

In a study by Hashmi et al., Ki-67 index in several intrinsic and histological types of breast cancer was evaluated; a high Ki-67 index was found in HER2/neu and triple-negative intrinsic breast cancer subtypes and metaplastic and medullary breast cancer types. Thus, all categories of breast cancer were regarded as aggressive phenotypes. In addition, tumor grade, considered a prognostic factor in breast cancer, was significantly related with Ki-67 index [12]. In the present study, the Ki-67 index was higher in patients aged >50 years, although it was relatively low in intraductal papilloma overall.

This study has several limitations: the sample size was small, the design was retrospective, and long-term follow-ups were missing.

Conclusions

In conclusion, p16 and p53 had a high rate of positivity in intraductal papilloma. While there was no difference in the distributions of p16 and p53 between age groups, the Ki-67 index was higher in patients aged >50 years. Multicentre studies with long-term follow-ups are needed to reveal the prognostic significance of the tumour-suppressing genes p16 and p53.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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